CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Tembotrione

Chemical Code # 6021, **Tolerance #** 53105
SB 950 # NA

July 18, 2011

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect (non-oncogenic)
Reproduction, rat:	No data gap, possible adverse effect (non-reproductive**)**
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicated

Toxicology one-liners are attached.

All record numbers through #255869 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T110718
Revised by T. Moore, 7/18/11

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

53105-0040; 251760; "Chronic Toxicity and Carcinogenicity Study of AE0172747 in the Wistar Rat by Dietary Administration"; (P. Kennel; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 02055; 5/20/05); Sixty Wistar rats/sex/group were scheduled to be fed 0, 2, 20, 2500 or 5000 ppm of AE 0172747 (tembotrione technical) (batch no. PFI 0195; purity: 95%) in the diet for 24 months (carcinogenicity cohort). Another 10 animals/sex/group were to be euthanized after 52 weeks of treatment as the chronic toxicity cohort. In addition another 15 animals/sex/group in the control and 5000 ppm groups were in a recovery cohort and were to be treated for 52 weeks and then maintained on a standard diet for an additional 13 weeks. However, all of the males in the 5000 ppm group died or were euthanized by day 41 for humane reasons. In the 2500 ppm group, 34 of the 70 males had died or been euthanized for humane reasons by week 43. Due to the excessive mortality suffered by the males in the higher treatment groups, all of the males were removed from the study by week 44. The dietary intake of the active ingredient by the males for the 44-week treatment period was 0.09, 0.95 and 123.9 mg/kg/day for the 2, 20 and 2500 ppm groups, respectively. For the females over the 24 month period, the a.i. intake was 0.10, 1.05, 134 and 280 mg/kg/day for the 2, 20, 2500 and 5000 ppm treatment groups, respectively. The mean body weights of both sexes in the 2500 and 5000 ppm groups were less than those of the control group(NS, $p< 0.01$) (at least until the males were removed from the study). The mean food consumption of both sexes in the 5000 ppm group was less than that of the control during the 1st 6 weeks of the study. In the ophthalmological examination, a dose-related increase in the incidence of corneal opacity and neovascularization of the cornea was noted in the both sexes of the 20 and 2500 ppm groups and in the 5000 ppm females at 3-4 and 6-7 months of treatment and in the 2 ppm males at 6-7 months of treatment. In the recovery cohort, only 1 of the 15 females in the 5000 ppm group still exhibited corneal opacity after 13 weeks of non-treatment. However, nine of these females had corneal neovascularization. In the hematology evaluation, the red blood cell counts, hemoglobin concentrations and hematocrit values were affected at various times during the study for either of the sexes at 2500 or 5000 ppm. However, no physiologically relevant effects were noted. In the clinical chemistry, serum total bilirubin in the 2500 ppm males and cholesterol levels in the 2500 males and 5000 ppm females were elevated at various times during the study (NS, $p< 0.01$). In the urinalysis, the pH values for both sexes in the 20 ppm group and above were less than the control values throughout much of the study (NS, $p<0.05$ or 0.01). Likewise, an increased presence of ketones were noted in the urine of these same groups. In the necropsy, the mean absolute and relative liver weights of the 5000 ppm females and the relative liver weights in the 2500 ppm females in the carcinogenicity cohort were greater than the control values ($p<0.05$ or 0.01). The mean relative liver weights of the 5000 ppm females in the chronic toxicity and recovery cohorts were greater than the respective control values as well ($p<0.05$ or 0.01). In the histopathological examination of the females in the carcinogenicity cohort, an increased incidence in atrophy of the adrenal gland was noted for the 5000 ppm females. An increased incidence of keratitis in the eye of the 20 ppm females and above was evident. A treatment-related increase in biliary hyperplasia and fibrosis was noted in the livers of the 20 ppm females and above. Treatment-related increases in atrophy, chronic inflammation and vascular mineralization of the sciatic nerve were evident in the 2500 and/or 5000 ppm females. A concomitant atrophy was noted in the skeletal muscle of the 5000 ppm females. Acinar atrophy/fibrosis in the spleen was also evident for the 2500 and 5000 ppm females. **Possible adverse effects:** corneal opacity and neovascularization of the cornea in the eye; atrophy of the sciatic nerve. **Rat Chronic Dietary Toxicity NOEL:** (M) < 2 ppm (<0.09 mg/kg/day) (based upon the ocular lesions noted for the 2 ppm males), (F) 2 ppm (0.10 mg/kg/day) (based upon the ocular lesions noted of the 20 ppm females); **no oncogenicity was evident for the females; Study supplemental** (only females were included in the completed study). (Moore, 8/19/10)

53105-0041; 251762; "Chronic Toxicity and Carcinogenicity Study of AE 0172747 in the Male Wistar Rat by Dietary Administration"; (P. Kennel; Bayer CropScience, BP 153, 06903 Sophia

Antipolis Cedex, France; Study No. SA 02400; 11/7/05); Sixty male Wistar rats/group received 0, 1, 20, 200 or 800 ppm of AE 0172747 (tembotrione technical) (batch no. PFI 0195; purity: 95%) in the diet for 24 months (carcinogenicity cohort) (0, 0.04, 0.79, 8.3, 31.7 mg/kg/day). Another 10 animals/group were euthanized after 52 weeks of treatment as the chronic toxicity cohort. In addition, another 15 animals/group in the control and 800 ppm groups were in a recovery cohort and were treated for 52 weeks and then maintained on a standard diet for an additional 13 weeks. Survival of the treated animals was not affected. The mean body weights of the 20 ppm males and above were less than the control values by the end of the study ($p<0.01$). The mean food consumption of the males in the 800 ppm group was less than that of the control group during the first 2 to 3 months of the study. Thereafter, food consumption was not affected by the treatment. The hematology evaluation did not demonstrate any toxicologically-significant effects on any of the parameters. In the clinical chemistry evaluation, the serum cholesterol levels were elevated for the 200 and 800 ppm groups throughout the study (NS, $p<0.01$). For the animals in the recovery cohort, the serum cholesterol and globulin concentrations of the 800 ppm animals were greater than the control values after the 3-month recovery period ($p<0.01$). In the urinalysis, the pH values for the 20 ppm group and above were less than the control values throughout much of the study (NS, $p<0.05$ or 0.01). Likewise, an increased presence of ketones were noted in the urine of these same groups. In the ophthalmological examination, opacity, edema and neovascularization of the cornea were noted in 20, 200 and 800 ppm groups at all of the observation time points. In the recovery cohort, all fifteen of the animals in the 800 ppm group demonstrated corneal neovascularization at the conclusion of the 13-week recovery period. In the necropsy, the mean relative liver and kidney weights of the 20, 200 and 800 ppm groups in the carcinogenicity cohort were greater than the control values ($p<0.01$). In the histopathological examination, an increased incidence of keratitis in the eye of the 20 ppm group and above was evident in both the chronic toxicity and carcinogeneity cohorts. Corneal squamous cell carcinoma was noted for 4/60 and 2/60 animals in the 200 and 800 ppm groups, respectively. An increased incidence of retinal degeneration was evident for the 800 ppm group. Treatment with the test material increased the incidence of chronic nephropathy in the kidneys, colloidal alteration and pigmentation in the thyroid glands and degeneration/atrophy in the sciatic nerve of the 20 ppm group and above. The incidence of acinar atrophy/fibrosis of the pancreas and cystic hyperplasia of the thyroid gland was increased for the 200 and 800 ppm groups. **Possible adverse effects:** opacity and neovascularization of the cornea and retinal degeneration of the eye; corneal squamous cell carcinoma; **Rat Chronic Dietary Toxicity NOEL:** (M) 1 ppm (0.04 mg/kg/day) (based upon lesions in the eye of the 20 ppm males); **Study supplemental.** (Moore, 8/24/10)

CHRONIC TOXICITY, RAT

See Combined Rat above.

CHRONIC TOXICITY, DOG

**** 53105-0038; 251757**; "AE0172747: Chronic Toxicity Study in the Dog by Dietary Administration"; (P. Kennel; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 03352; 9/9/05); Four beagle dogs/sex/group received 0, 75, 300 or 1200 ppm of AE 0172747 (tembotrione technical) (batch no. PFI 0254; purity: 95.4%) in the diet for 12 months ((M) 0, 2.5, 9.0, 37.8 mg/kg/day, (F) 0, 2.5, 10.2, 41.6 mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption of the study animals was not apparently affected by the treatment. In the hematology evaluation, the calculated values for the mean corpuscular volume, mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration of the 1200 ppm females were less than those of the control group at various times during the study (NS, $p<0.05$ or 0.01). The mean corpuscular hemoglobin values of the 1200 ppm males were less than those of the control males throughout the study (NS, $p<0.05$ or 0.01). In the evaluation of erythrocyte morphology in the 1200 ppm group, anisocytosis, microcytosis, anisochromia and/or hypochromia were noted for all of the females and one of the males by the termination of the study. The observed effects ranged from slight to severe. The mean platelet count for both sexes in the 1200 ppm group was greater than that of the control group throughout the treatment period (NS, $p<0.05$ or 0.01). However, the clotting parameters were not affected. Serum alkaline phosphatase activity was elevated for the females in the 1200 ppm group throughout the treatment period (NS or $p<0.01$). Ketones were present in the urine of both sexes

in all of the treatment groups throughout the study. However, the severity of the response did not demonstrate a treatment-relationship. In the necropsy, the mean absolute liver weights of both sexes in all of the treatment groups were greater than the control values (NS, $p<0.05$ or 0.01). Only the mean relative weight of the 1200 ppm females was statistically greater than the control value ($p<0.05$). This observation correlated with the incidence of minimal to slight hepatocellular hypertrophy in all four of these animals. In the thyroid gland, golden brown pigments were observed in the follicular cells of 3 females in the 1200 ppm group and 1 female in the 300 ppm group. An increased presence of unilateral/bilateral digestion chambers in the sciatic nerves of the one male each in the 75 and 300 ppm groups and two males in the 1200 ppm group. However, the severity of the effect was not increased in a treatment-related manner. **Possible adverse effect:** blood dyscrasia. **Dog Chronic Dietary Toxicity NOEL:** (M/F) 300 ppm ((M) 9.0 mg/kg/day, (F) 10.2 mg/kg/day) (based upon the treatment-related effects on erythrocyte morphology in both sexes of the 1200 ppm group); **Study acceptable.** (Moore, 8/11/10)

ONCOGENICITY, RAT

See Combined Rat above.

ONCOGENICITY, MOUSE

**** 53105-0039; 251758**; "Carcinogenicity Study of AE0172747 in the C57BL/6 Mouse by Dietary Administration"; (C. Langrand-Lerche; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 02256; 9/9/05); Fifty C57BL/6J mice/sex/group received 0, 30, 300, 1000 or 3000 ppm of AE 0172747 (tembotrione technical) (batch no. PFI 0195; purity: 95%) in the diet for 18 months ((M) 0, 4.33, 43.2, 145.9, 439.6 mg/kg/day, (F) 0, 5.41, 54.0, 179.1, 552.3 mg/kg/day). Another 10 animals/sex/group were treated for 12 months and euthanized at that time. Survival of the study animals was not affected by the treatment. The mean body weights of the 3000 ppm females were less than those of the control group at various times during the study. No treatment-related effect on food consumption was noted for the males. The mean food consumption of the 3000 ppm females was less than that of the control group at various times over the course of the study ($p<0.05$ or 0.01). The animals in the 1000 and 3000 ppm groups excreted intense yellow colored urine after 3 to 5 months of treatment. No treatment-related lesions were noted in the ophthalmology examination throughout the study. In the hematology evaluation, the red blood cell count, hemoglobin concentration and hematocrit of the 3000 ppm females were less than the control values at both 12 and 18 months of treatment (NS, $p<0.01$). The values for these same parameters were less than those of the control group for the females in the other treatment groups at 18 months as well ($p<0.01$). In the necropsy examination, the mean absolute and relative liver weights of both sexes in the 30 ppm treatment group and above were greater than the control values after 18 months of treatment (NS, $p<0.01$). In the histopathology, diffuse centri- to panlobular hypertrophy was noted in the livers of both sexes in the 300, 1000 and 3000 ppm groups after 12 and 18 months of treatment. This effect was also evident in the livers of the 30 ppm females. Other hepatic effects included focal/multifocal hepatocellular degeneration which was noted in both sexes of the 1000 and 3000 ppm groups and the females in the 300 ppm group. An increased incidence of gallstones was evident for both sexes in the 30 ppm group and above after 18 months of treatment. **Possible adverse effect:** hepatocellular degeneration in the liver; **Mouse Chronic Dietary Toxicity NOEL:** (M/F) < 30 ppm ((M): < 4.33 mg/kg/day, (F) < 5.41 mg/kg/day) (based upon the presence of hepatocellular hypertrophy and/or gallstones in the liver of both sexes in the 30 ppm group); **oncogenicity was not evident. Study acceptable.** (Moore, 8/13/10)

REPRODUCTION, RAT

**** 53105-0037; 251756**; "Technical Grade AE0172747: A Two-Generation Reproductive Toxicity Study in the Wistar Rat"; (A.D. Young, B.L. Fickbohm; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201266; 8/31/05); Thirty rats/sex/group in the F0 generation received 0, 20, 200, or 1500 ppm of AE 0172747 (tembotrione technical) (batch no. OP2250027; purity: 94.0%) in the diet for a 10-week premating period, up to 2 weeks during the mating period and for 3 weeks both for the gestation and lactation periods. The 30 F1 animals/sex/group which were selected as parents, were treated for 10 weeks during the premating period, followed by mating and 3 weeks each for gestation and lactation of the F2 generation (F0 generation: (M) 0, 1.4,

13.1, 98.2 mg/kg/day, (F) 0, 1.6 to 3.3, 15.4 to 31.0, 115.4 to 227.2 mg/kg/day, F1 generation: (M) 0, 1.3, 13.5, 102.5 mg/kg/day, (F) 0, 1.5 to 3.2, 14.8 to 30.7, 110.7 to 228.1 mg/kg/day). The F0 parental females in the 200 and 1500 ppm groups had lower mean body weights than the control animals after 10 weeks of treatment during the premating period ($p<0.01$ or 0.05). The F0 high dose females also demonstrated a lower mean body weight during week 2 of the lactation period ($p<0.01$). The mean food consumption of the 200 and 1500 ppm females during the lactation period, week 2, was less than that of the control females in the F0 generation ($p<0.01$). The mean body weight of the F0 generation 1500 ppm males was less than that of the control group after 10 weeks of treatment (NS). In the F1 generation, the mean food consumption of the 1500 ppm females during week 2 of lactation was less than that of the control group ($p<0.01$). The mean body weights of the 200 and 1500 ppm males were less than the control group value after 10 weeks of treatment during the premating period ($p<0.01$). Corneal opacity was noted for parental animals in all of the treatment groups in both generations. For the animals retained as F1 and F2 generation juveniles, the onset of corneal opacity was noted between days 31 and 50, days 28 and 48 and days 23 and 53 post-weaning for the 20, 200 and 1500 ppm groups, respectively in the F1 generation and between days 34 and 53, days 26 and 52 and days 23 and 52 post-weaning for the 20, 200 and 1500 ppm groups, respectively, for the F2 generation. In the histopathological evaluation of the parental animals, inflammation and neovascularization of the eye was noted for both sexes in all of the treatment groups of both generations. Similarly, in the 21-day old pups of the F1 generation and in the juveniles of the F2 generation, inflammation and neovascularization of the eye was noted. No treatment-related effect was evident for the mating and other reproductive parameters. The mean F1 pup weights in the 200 and 1500 ppm groups were less than the control values over the last 2 weeks of the lactation period ($p<0.01$). The mean F2 pup weights of the 200 and 1500 ppm groups were less than that of the control group by the end of the lactation period ($p<0.01$). Pup viability was not affected in either generation. Preputial separation was delayed in treatment-related manner for all of the treatment groups in both generations ($p<0.01$). The time to vaginal opening of the F1 female offspring in the 1500 ppm group was delayed ($p<0.5$). This effect was not noted for the F2 generation. No treatment-related effect was noted on sperm motility, sperm counts or sperm morphology in either generation. **Possible adverse effects:** corneal opacity and neovascularization of the eye (non-reproductive). **Parental NOEL:** (M/F) <20 ppm ((M) <1.3 mg/kg/day, (F) <1.6 mg/kg/day)(based upon ocular pathology for both sexes in the 20 ppm group); **Reproductive NOEL:** 1500 ppm ((M) 102.5 mg/kg/day, (F) 123.1 mg/kg/day) (based upon the lack of a treatment-related effect in the 1500 ppm group);**Developmental NOEL:** 20 ppm ((F) 3.2 mg/kg/day)(based upon lower mean pup weights in the 200 ppm group during the lactation period of both generations); **Study acceptable.** (Moore, 8/9/10)

TERATOLOGY, RAT

** 53105-0034; 251751; “AE 0172747: Developmental Toxicity Study in the Rat by Gavage”; (S. Wason; Bayer CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 02226; 9/4/03); Twenty five mated female Sprague-Dawley rats were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose 400), 25, 125 or 500 mg/kg/day of AE 0172747 (tembotrione technical) (batch no. PFI0195; purity: 95.0%) from gestation day 6 through gestation day 20. No maternal deaths occurred during the study. The mean body weight gains of the 25 mg/kg dams and above were less than that of the control group between days 6 and 8 of gestation ($p<0.05$ or 0.01). Mean food consumption was reduced for the dams in the 125 and 500 mg/kg treatment groups between days 6 and 12 of gestation ($p<0.05$ or 0.01). Increased salivation was noted for the dams in the 500 mg/kg group. The mean fetal weights of the 25 mg/kg group and above were less than that of the control group ($p<0.01$). An increased incidence of delayed ossification was noted in the 25 mg/kg group and above. **No adverse effect indicated. Maternal NOEL:** < 25 mg/kg/day (based upon lower body weight gain between gestation days 6 and 8 in the 25 mg/kg group); **Developmental NOEL:** < 25 mg/kg/day (based upon the higher incidence of delayed ossification in the skeletal bones of the 25 mg/kg fetuses); **Study acceptable.** (Moore, 7/28/10)

Range-finding Teratology Studies

53105-0033; 251750; "AE 0172747: Range-Findng Study for Developmental Toxicity in the Rat by Gavage"; (S. Wason; Aventis CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 01280; 1/7/02); Eight mated Sprague-Dawley female rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose 400), 10, 25, 75, 200 or 400 mg/kg/day of AE 0172747 (tembotrione technical) (batch no. LE 356; purity: 97.4%) from gestation day 6 through gestation day 20. No maternal deaths resulted from the treatment. The mean body weight gain of the dams in the 200 and 400 mg/kg groups was reduced between gestation day 6 and 8. Increased salivation was noted for all of the dams in the 400 mg/kg group and for 2 dams in the 200 mg/kg group during the latter stage of the dosing period. There was no treatment-related effect upon the various litter parameters. The mean body weight of the fetuses in the 400 mg/kg group was less than that of the control. **No adverse effect indicated. Maternal NOEL:** 75 mg/kg/day (based upon reduced body weight gain between gestation day 6 and 8 and incidence of increased salivation in the 200 mg/kg dams); **Developmental NOEL:** 200 mg/kg/day (based upon the lower mean fetal weight in the 400 mg/kg group); **Study supplemental.** (Moore, 7/27/10)

TERATOLOGY, RABBIT

**** 53105-0035; 251754**; "AE 0172747:Developmental Toxicity Study in the Rabbit by Gavage"; (S. Wason; Bayer CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 02056; 2/24/03); Twenty five mated New Zealand White female rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose 400), 1, 10, or 100 mg/kg/day of AE 0172747 (tembotrione technical) (batch no. PFI0195; purity: 95.0%) from gestation day 6 through gestation day 28. One doe in the 100 mg/kg group died on gestation day 15, three more were euthanized for humane reason between gestation days 16 and 22 and a fifth doe in this group suffered an abortion. One doe in the 10 mg/kg group aborted on day 23 and one doe in the 1 mg/kg group was euthanized on day 21 for humane reasons. The mean body weight gain of the does in the 100 mg/kg group was less than that of the control group between gestation days 6 and 14 ($p<0.05$). The mean food consumption of the does in this group was also less than that of the control group during this period. There was a greater incidence of various fetal skeletal anomalies and variations in the 10 and 100 mg/kg groups. **Possible adverse effect:** increased incidence of skeletal anomalies. **Maternal NOEL:** 10 mg/kg/day (based upon the lower body weight gain and an increased number of deaths in the 100 mg/kg group); **Developmental NOEL:** 1 mg/kg/day (based upon the higher incidence of fetal skeletal anomalies and variations in the 10 mg/kg group); **Study acceptable.** (Moore, 7/30/10)

Range-finding Teratology Studies

53105-0034; 251752; "AE 0172747: Range-Finding Study for Developmental Toxicity Study in the Rabbit by Gavage"; (S. Wason; Bayer CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 01279; 2/18/03); Eight mated New Zealand White female rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose 400), 3, 10, 25, 75, or 250 mg/kg/day of AE 0172747 (tembotrione technical) (batch no. LE 356; purity: 97.4%) from gestation day 6 through gestation day 28. Three does in the 250 mg/kg group were found dead on day 14. The remaining five animals in this group were euthanized for humane reasons between gestation days 13 and 16. The mean body weight gain of the does in the 75 mg/kg group was less than that of the control group between gestation days 6 and 14. The mean food consumption of the does in this group was also less than that of the control group during this treatment period. There was an increased number of dead fetuses in the 75 mg/kg group. The mean weight of the fetuses in the 75 mg/kg was less than that of the control group (NS). **No adverse effect indicated. Maternal NOEL:** 25 mg/kg/day (based upon the lower body weight gain and food consumption demonstrated by the females in the 75 mg/kg group); **Developmental NOEL:** 25 mg/kg/day (based upon the higher incidence of fetal death and lower mean fetal weights in the 75 mg/kg group); **Study supplemental.** (Moore, 7/29/10)

53105-0035; 251753; "AE 0172747: Complementary Range-Finding Study for Developmental Toxicity Study in the Rabbit by Gavage"; (S. Wason; Bayer CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 02041; 2/17/03); Eight mated New Zealand White female rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose

400) or 125 mg/kg/day of AE 0172747 (tembotrione technical) (batch no. PFI0195; purity: 95.0%) from gestation day 6 through gestation day 28. One doe in the 125 mg/kg group was euthanized for humane reasons on gestation day 22. The mean body weight gain of the does in the 125 mg/kg group was less than that of the control group between gestation days 6 and 14. The mean food consumption of the does in this group was also less than that of the control group during this treatment period. The mean weight of the fetuses in the 125 mg/kg was less than that of the control group (NS). **No adverse effect indicated. Maternal NOEL:** <125 mg/kg/day (based upon the lower body weight gain and food consumption demonstrated by the females in the 125 mg/kg group); **Developmental NOEL:** < 125 mg/kg/day (based upon the mean fetal weights in the 125 mg/kg group); **Study supplemental.** (Moore, 7/29/10)

GENE MUTATION

** 53105-0042; 251766; "Technical AE 0172747: Bacterial Reverse Mutation Test"; (K. May; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. AES 117/023631; 10/10/03); In the first trial, *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2*uvr*A/pKM101 (CM891) were exposed to Technical AE 0172747 (lot no. PFI 0215; purity: 94%) at concentrations ranging from 5 to 5000 ug/plate for 72 hours at 37^{o} C, using the plate incorporation technique. In the 2nd trial, the same strains were exposed to concentrations of the test material ranging from 50 to 5000 ug/plate for 30 minutes at 37^{o} during a pre-incubation period followed by exposure for 72 hours at 37^{o} C. Both trials were performed under conditions of non-activation and activation. There were 3 plates per treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/25/10)

** 53105-0043; 251770; "Technical AE 0172747: Mammalian Cell Mutation Assay"; (K. May; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. AES 119/024223; 1/25/05); Chinese Hamster Ovary cells (CHO-K1) were exposed to concentrations of Technical AE 0172747; lot no. PFI 0215; purity: 94% ranging from 250 to 1600 ug/ml for 4 hours at 37^{o} C under conditions of activation and non-activation in the two trials. Duplicate cultures were performed for each treatment level (four cultures for the solvent control). The S9 fraction used to metabolize the test material was derived from the livers of male Sprague-Dawley rats pretreated with Aroclor 1254. An increased rate of mutation was not consistently demonstrated at any treatment level with or w/o activation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/30/10)

CHROMOSOME EFFECTS

**** 53105-0043; 251774**; "Technical AE 0172747: *In Vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes"; (C. Mason; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. AES 118/024021; 1/6/04); Primary human lymphocyte cultures in whole blood (stimulated with PHA for 48 hours), procured from healthy male volunteers, were treated with concentrations of Technical AE 0172747 (lot no. PFI 0215; purity: 94.0%) ranging from 0.08 to 10 mM under conditions of nonactivation and activation for 3 hours, followed by a recovery period of 16 hours of incubation in Trial No. 1. In Trial No. 2, the cells were treated with concentrations of the test material ranging from 1.25 to 10.0 mM for 3 hours under conditions of non-activation and activation, followed by a recovery period of 16 hours. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases/replicate were examined for structural abnormalities. A treatment-related increase in chromosomal aberrations was evident under conditions of activation when the relative mitotic index was less than 50%. The positive controls were functional. **Possible adverse effect**: increased clastogenicity under conditions of activation. **Study acceptable.** (Moore, 9/1/10)

DNA DAMAGE

** 53105-0044; 251778; "Technical AE 0172747: Mouse Micronucleus Test"; (Z. Mehwood; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England;

Study No. AES 120/023519; 10/27/03); Seven male CD1 mice/group were dosed orally by gavage with 0 (1% CMC), 500, 1000 or 2000 mg/kg of Technical AE 0172747 (lot no. PFI0215; purity: 94.0%). An additional 7 males/group were dosed with 0 or 2000 mg/kg of the test material. Five males were dosed orally with 12 mg/kg of Mitomycin C. Seven animals/group were euthanized at 24 hours post-dose (note: this included the 5 animals in the positive control group as well). The remaining 7 animals/group in the control and 2000 mg/kg groups were euthanized at 48-hours post-dose. The incidences of micronucleated polychromatic (PCE) and normochromatic (NCE) erythrocyctes and the percentage of PCEs in the total erythrocyte population were reported. There was no treatment-related increase in the percentage of micronucleated PCEs. No unscheduled deaths occurred during the study. The animals in the 2000 mg/kg group demonstrated hunched posture, reduced activity, fast and irregular respiration and piloerection. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 9/8/10)

** 53105-0044; 251779; "Technical AE 0172747: Unscheduled DNA Synthesis Test with Rat Liver Cells *In Vivo*"; (U. Wirnitzer; Bayer HealthCare AG, PH-R&D-Toxicology International, Genetic Toxicology, 42096 Wuppertal, Germany; Report No. AT02169; 7/1/05); Eight Sprague-Dawley male rats/group received a single oral dose of 0 (aqueous 0.5% cremophor), 1000 or 2000 mg/kg of Technical AE 0172747 (lot no. Tox AE 747-2004-12-06; purity: 94.1%) by gavage. Hepatocytes from 4 animals/group/time point were isolated at 4 and 16 hours post-dosing. Viability was determined by trypan blue dye exclusion and ranged from 69.1% to 83.8%. After attachment, cells were exposed to (methyl-^{3}H) thymidine for 4 hours followed by an overnight incubation with unlabelled thymidine. Three slides per animal were scored, 50 cells per slide. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. Positive controls were functional. **Study Acceptable**. (Moore, 9/8/10).

NEUROTOXICITY

Acute Neurotoxicity Study

** 53105-0045; 251780; "An Acute Oral Neurotoxicity Screening Study with Technical AE 0172747 in Wistar Rats"; (L.P. Sheets, R.G. Gilmore, L.E. Elcock; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201248; 4/5/05); Twelve Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose/0.4% Tween 80), 200, 500 or 2000 mg/kg of Technical AE 0172747 (batch no. PFI 0215; purity: 94.0%). One male in the 2000 mg/kg group was found dead on day 4. Death was due to a perforated esophagus. In the open field evaluation of the FOB, an increased number of animals of both sexes in the 2000 mg/kg group demonstrated reduced arousal at 3 hours post-dose (NS, $p<0.05$). Both sexes in the 2000 mg/kg group had a lower mean number of rearings at 3 hours post-dose as well (NS, $p<0.05$). In the physiological/reflex evaluation, an increased number of males in the 2000 mg/kg group had no reaction in the approach response at 3 hours post-dose ($p<0.05$). The mean body temperatures of both sexes in the 2000 mg/kg and of the females in the 500 mg/kg group were less than the control values at 3 hours post-dose ($p<0.05$). The mean motor and locomotor activities of both sexes in the 500 and 2000 mg/kg groups were less than those of the control group at 3 hours post-dose ($p<0.05$). No treatment-related effects were evident at 7 days post-dose. No treatment-related effect on brain weight was noted in the necropsy examination. In the histopathological examination, no treatment-related lesions were evident in the neurological tissues. **No adverse effect indicated. Rat Acute Neurotoxic NOEL:** (M/F) 200 mg/kg (based upon the reduced motor and locomotor activity noted for the 500 mg/kg treatment group); **Study acceptable.** (Moore, 9/13/10)

Rat Subchronic Neurotoxicity Study

** 53105-0046, -0052; 251781, 251804; "A Subchronic Neurotoxicity Screening Study with Technical Grade AE 0172747 in Wistar Rats"; (R.G. Gilmore, L.E. Elcock; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201174; 3/28/05); Twelve Wistar rats/sex/group received 0, 20, 250 or 2500 ppm of Technical AE 0172747 (batch no. PFI 0215; purity: 94.0%) in the diet for 13 weeks ((M) 0, 1.33, 16.4, 160 mg/kg/day, (F) 0, 1.75, 21.0, 224 mg/kg/day). One female in

the 2500 ppm group died prior to the initiation of the study. She was not replaced with another animal. The mean body weights of both sexes in the 2500 ppm group were lower than those of the control group over the course of the study (NS, $p<0.05$). The mean food consumption of the 2500 ppm males was less than that of the control group (NS). The Functional Observational Battery and motor activity assessment and the ophthalmological examination did not reveal any treatment-related effects. In the necropsy examination, no treatment-related effect was noted upon the brain weights. In the histology examination, no treatment-related lesions were noted in the neurological tissues. **No adverse effect indicated. Rat Subchronic Neurotoxic NOEL:** (M/F): 2500 ppm ((M) 160 mg/kg/day, (F) 224 mg/kg/day) (based upon the lack of treatment-related neurotoxic effects noted for the animals in the 2500 ppm group); **Study acceptable.** (Moore, 9/21/10)

Rat Developmental Neurotoxicity Study

** 53105-0047; 251782; "A Developmental Neurotoxicity Screening Study with Technical Grade AE 0172747 in Wistar Rats"; (L.P. Sheets, R.G. Gilmore, H.E. Hoss; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201310; 7/7/05); Thirty mated female Wistar rats/group received 0, 10, 200 or 1500 ppm of Technical AE 0172747 (batch nos. PFI 0215, OP2250027, purity: 94.0%) in the diet from day 6 of gestation through day 21 of lactation (0, 0.8, 16.3, 118 mg/kg/day). The concentration of the test material in the feed was adjusted in order to maintain a constant level of a.i. uptake over the course of the dosing period. Offspring from 23 litters in the control and 200 ppm groups, 22 litters in the 10 ppm group and 20 litters in the 1500 ppm group were assessed neurologically up to 70 days post-natal in the functional observational battery (FOB), measurement of motor activity, auditory startle response, passive avoidance learning and memory and water maze learning and memory assessments. The neuropathologic examination and morphometric analysis of selected neurological tissues from the pups were performed. One dam in the 1500 ppm group was found dead on gestation day 15. The mean body weights and food consumption of the 200 and 1500 ppm dams were less than the control group values throughout much of the gestation and lactation periods ($p<0.05$ or 0.01). The mean body weights of the 200 and 1500 ppm pups and young adult animals of both sexes were less than those of the control group ($p<0.05$ or 0.01). There was no treatment-related effect on the live birth, viability or lactation indices. The preputial separation of the 1500 ppm male pups was delayed ($p<0.01$). In the FOB, the 200 and 1500 ppm dams suffered corneal opacity by the end of the treatment period. For the pups, the amplitude of the acoustic startle response was less for both sexes in the 60-day old cohort of the 200 and 1500 ppm groups (NS, $p<0.05$). No other treatment-related effects were noted in the FOB for the pups. The motor activity assessment of the pups did not reveal any treatment-related effects. The passive avoidance learning and memory and water maze learning and memory assessments did not indicate any treatment-related effects on the pups. In the necropsy examination, although the mean absolute brain weights of the 200 and 1500 ppm pups and young adults were less than the control values, the mean relative weights were not affected by the treatment. No neuropathological lesions were noted in either the 21-day old pups or the 70-day old adults. Morphometric analysis of the brain of these animals did not demonstrate any treatment-related effects. **No adverse effect indicated. Maternal NOEL:** 10 ppm (0.8 mg/kg/day) (based upon the lower mean body weights and the incidence of corneal opacity in the 200 ppm dams); **Developmental Neurotoxicity NOEL:** 10 ppm (0.8 ppm) (based upon the lower amplitude noted for the young adults in the acoustic startle response)**; Study acceptable.** (Moore, 9/27/10)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Studies

**** 53105-0058; 251818**; "AE 0172747: 90-Day Toxicity Study in the Rat by Dietary Administration"; (G. Steiblen; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 01170; 11/15/02); Ten Wistar rats/sex/group received 0, 1.25, 75, 1500 or

7000 ppm of AE 0172747 (tembotrione technical) (batch no. LE356; purity: 97.4%) in the diet for 13 weeks ((M) 0, 0.07, 4.45, 86.4, 413 mg/kg/day, (F) 0, 0.08, 5.59, 107.2, 465 mg/kg/day). In addition, 5 animals/sex in the 75 and 1500 ppm groups were included in a recovery cohort. Their eyes were examined 4 weeks after termination of treatment. One male in the 7000 ppm group was euthanized for humane reasons on day 64. The mean body weights of both sexes in the 7000 ppm group and the males in the 1500 ppm group were less than the control values throughout the study (NS, $p<0.01$ or 0.001). The mean food consumption of both sexes in the 7000 ppm group was less than that of the control group throughout the study (NS, $p<0.05$, 0.01 or 0.001). In the ophthalmology examination, corneal opacity was noted in both sexes of the 75, 1500 and 7000 ppm groups by the end of the treatment period ((M) 0: 0/10 vs. 75: 2/15, 1500: 4/15, 7000: 2/10, (F) 0: 0/10 vs. 75: 1/15, 1500: 4/15, 7000: 2/10). Neovascularization of the cornea was evident in both sexes of the 75 and 1500 ppm groups and in the males of the 7000 ppm group at the end of the treatment ((M) 0: 0/10 vs. 75: 2/15, 1500: 4/15, 7000: 2/10, (F) 0: 0/10 vs. 75: 1/15, 1500: 3/15, 7000: 0/10). In the recovery cohort 2 of the 5 males in the 1500 ppm group still demonstrated neovascularization in their corneas after 4 weeks. In the hematology evaluation, the red blood cell count, hemoglobin concentration and the hematocrit of the 7000 ppm males were less than the control values ($p<0.05$, 0.01 or 0.001). The mean corpuscular volume and mean corpuscular hemoglobin of these males were greater than the control group values ($p<0.001$). The mean prothrombin and mean activated partial thromboplastin (APT) times of the 7000 ppm males and the APT times of the 1500 and 7000 ppm males were greater than the times of the control group ($p<0.05$, 0.01 or 0.001). In the clinical chemistry evaluation, the mean serum cholesterol levels of both sexes in the 7000 ppm group and the males in the 75 and 1500 ppm groups were greater than the control values ($p<0.01$ or 0.001). The mean triglyceride, serum albumin and total protein levels of the males in the 75, 1500 and 7000 ppm groups were significantly affected by the treatment, but dose-related changes in the values were not evident. In the urinalysis, the urine pH of both sexes in the 1500 and 7000 ppm groups and the females in the 75 ppm group was less than the control values (NS, $p<0.05$, 0.01). An increased level of ketones in the urine was noted for both sexes in the 75 ppm group and above. In the necropsy, the mean absolute and relative liver weights of the 75 ppm males and above and the mean relative liver weight of the 7000 ppm females were greater than the control group values ($p<0.01$ or 0.001). The mean relative kidney weights of the 1500 and 7000 ppm males were greater than that of the control group ($p<0.05$ or 0.001). In the histopathology examination, hepatocellular hypertrophy was noted in the livers of the males in the 75, 1500 and 7000 ppm groups. In the submaxillary lymph nodes of the 7000 ppm males, erythrophagocytosis and paracortical hyperplasia were evident (other treatment groups were not examined). An increase in the accumulation of golden-brown pigments in the pancreas and megacaryocytosis and increased erythropoiesis in the bone were noted for the 7000 ppm males. These effects were attributed to the treatment-related effect on the red blood cells. An increased incidence of unilateral and/or bilateral atrophy of the testes was noted for males in the 7000 ppm group. For the females, basal, corticotubular vacuolation of the kidneys was evident for the 75, 1500 and 7000 ppm groups. Hypertrophy of the interstitial gland in the ovaries of the 1500 and 7000 ppm groups. **Possible adverse effect:** corneal opacity and neovascularization of the cornea; **Rat Subchronic Dietary Toxicity NOEL:** (M/F) 1.25 ppm ((M) 0.07 mg/kg/day, (F) 0.08 mg/kg/day) (based upon treatment-related effects on the cornea of both sexes in the 75 ppm group and the liver hypertrophy of the 75 ppm males); **Study acceptable.** (Moore, 9/20/10)

** 53105-0059; 251819; “AE 0172747: 90-Day Toxicity Study in the Rat by Dietary Administration”; (P. Kennel; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 05002; 10/28/05); Ten Wistar rats/sex/group received 0, 6, 20 or 40 ppm of AE 0172747 (tembotrione technical) (batch no. PFI 0254; purity: 94.7 to 95.4%) in the diet for 13 weeks ((M) 0, 0.30, 0.98, 2.20 mg/kg/day, (F) 0, 0.35, 1.18, 2.68 mg/kg/day). No unscheduled deaths occurred during the study. The mean body weights and food consumption of the study animals was not affected by the treatment. No treatment-related effects were evident in the neurotoxicity or hematology evaluations. In the ophthalmology examination, one female in the 40 ppm group suffered corneal opacity and neovascularization of the cornea. No other treated animals were affected. In the clinical chemistry evaluation, the mean total protein levels of the males in the 20 and 40 ppm groups were greater than the control value ($p<0.05$). In the

urinalysis, the urine pH of the males in the 40 ppm group was less than the control value ($p<0.05$). An increased level of ketones in the urine was noted for both sexes in the 6 ppm group and above. In the necropsy, the mean absolute and relative liver weights of both sexes in the 40 ppm group and the males in the 6 and 20 ppm groups were greater than the control group values ($p<0.05$ or 0.01). In the histopathology examination, hepatocellular hypertrophy was noted in the livers of the males in the 6, 20 and 40 ppm groups. **No adverse effect indicated. Rat Subchronic Dietary Toxicity NOEL:** (M/F) < 6 ppm ((M) < 0.30 mg/kg/day, (F) <0.35 mg/kg/day) (based upon treatment-related effects on the liver of the males and the increased ketone levels in the urine of both sexes in the 6 ppm group); **Study acceptable.** (Moore, 9/21/10)

Rat Repeated Dosing Dermal Toxcity Studies

** **53105-0031; 251748**; "AE 0172747: Subacute Toxicity Study in the Rat (4 Weeks Dermal Administration)"; (F. Krotlinger; Bayer HealthCare AG, PH-R&D Toxicology, 42096 Wuppertal, Germany; Report No. AT02011; 5/2/05); The skin of 10 Wistar rats/sex/group was exposed to 0, 250, 500 or 1000 mg/kg/day of AE 0172747 (batch no. PFI0254; purity: 95.4%) 6 hours/day, 22 or 23 days of treatment over a 30-day period. The test material was placed on a piece of gauze moistened with water and the gauze was placed on the skin. No deaths resulted from the treatment. The mean body weights, food consumption and water uptake were not affected by the treatment. The clinical chemistry and ophthalmology evaluations did not reveal any treatment-related effects. In the hematology evaluation, an increased percentage of reticulocytes was noted in all of the female treatment groups ($p<0.05$). However no other effects were evident in the hematology parameters. The mean absolute and relative liver weights of the 500 and 1000 mg/kg males and the mean relative liver weight of the 250 mg/kg males were greater than the control values ($p<0.05$ or 0.01). In the histopathology, there was an increased incidence and/or severity of degeneration/apoptosis in the pancreas of both sexes in the 250 mg/kg group and above. Ductular regeneration was noted in the pancreas of three females in the 1000 mg/kg group and one each of the two lower dose groups. An increased incidence of colloid alteration was evident in the thyroid gland of both sexes in all of the treatment groups. Hypertrophy of the follicular epithelium was noted for males in all of the treatment groups. Condensed cytoplasm and peripheral hypertrophy/change was evident in the livers of the 500 and 1000 mg/kg females. However, these effects were not manifested in a dose-related manner. Inflammation of the prostate was noted for the males in the 1000 mg/kg group. **Possible adverse effect:** increased incidence and severity of degeneration/apoptosis in the pancreas. **Rat 4-Week Repeated Dose Dermal Toxicity NOEL:** (M/F) < 250 mg/kg/day (based upon treatment-related effects noted in the pancreas and thyroid gland of both sexes in the 250 mg/kg treatment group); **Dermal Irritation NOEL:** (M/F) 1000 mg/kg/day (based on the lack of dermal irritation at the site of application on the 1000 mg/kg treatment group); **Study acceptable**. (Moore, 7/26/10)

** **53105-0033; 251749**; "AE 0172747: Subacute Toxicity Study in the Rat (4 Weeks Dermal Administration)"; (F. Krotlinger, L. Schladt; Bayer HealthCare AG, PH-R&D Toxicology, 42096 Wuppertal, Germany; Report No. AT02587; 11/9/05); The skin of 10 Wistar rats/sex/group was exposed to 0, 50, 250 or 1000 mg/kg/day of AE 0172747 (batch no. PFI0254; purity: 94.7%) 6 hours/day, 22 or 23 days of treatment over a 30-day period. The test material was placed on a piece of gauze moistened with water and the gauze was placed on the skin. No deaths resulted from the treatment. The mean body weights, food consumption and water uptake were not affected by the treatment. The hematology and ophthalmology evaluations did not reveal any treatment-related effects. In the clinical chemistry evaluation, the total protein was increased in the serum of the 250 and 1000 mg/kg males ($p<0.01$). The serum albumin levels were increased for the both sexes in the 250 and 1000 mg/kg groups and for the 50 mg/kg males ($p<0.05$ or 0.01). The mean relative liver weights of the 50, 250 and 1000 mg/kg males were greater than the control values ($p<0.05$ or 0.01). In the histopathology, there was an increased incidence and/or severity of degeneration/apoptosis in the pancreas of both sexes in the 250 and 1000 mg/kg group and in the 50 mg/kg males. An increased incidence of colloid alteration was evident in the thyroid gland of both sexes in the 250 and 1000 mg/kg groups and in the males of the 50 mg/kg group. Hypertrophy of the follicular epithelium was noted for females in the 250 and 1000 mg/kg groups. **Possible adverse effect:** increased incidence and severity of degeneration/apoptosis in the pancreas. **Rat 4-Week Repeated Dose Dermal Toxicity NOEL:**

(M) < 50 mg/kg/day (based upon treatment-related effects noted in the pancreas and thyroid gland of the males in the 50 mg/kg treatment group) (F) 50 mg/kg/day (based upon treatment-related effects noted in the pancreas and thyroid gland of the females in the 250 mg/kg treatment group) **Dermal Irritation NOEL:** (M/F) 1000 mg/kg/day (based on the lack of dermal irritation at the site of application on the 1000 mg/kg treatment group); **Study acceptable**. (Moore, 7/26/10)

Mouse Subchronic Dietary Study

53105-0028; 251745; "AE 0172747: 90-Day Toxicity Study in the Mouse by Dietary Administration"; (G. Steiblen; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 01431; 7/9/03); Ten C57BL/6J mice/sex/group received 0, 35, 350, 3500 or 7000 ppm of AE 0172747 (batch no. PFI0195; purity: 95.0%) in the diet for 13 weeks ((M) 0, 5.93, 64.0, 631, 1317 mg/kg/day; (F) 0, 7.33, 75.7, 783, 1833 mg/kg/day). One male in the 7000 ppm group was euthanized on day 78 for humane reasons. One female in the 3500 ppm group was found dead on day 56. No treatment-related effect was evident. The mean body weight of the 7000 ppm females was less than that of the control group at various time points during the study ($p<0.05$). There was no treatment-related effect upon the mean food consumption of the study animals. The mean serum alanine transaminase (ALAT) activity was increased in a dose-related manner for the 3500 and 7000 ppm males ($p<0.05$). The ALAT activity in the serum of the 3500 ppm females was greater than the control value ($p<0.05$). However, the effect was not evident in the serum of the 7000 ppm females. The serum urea concentration was increased for the 3500 and 7000 ppm males ($p<0.05$). The mean absolute and relative liver weights of both sexes in the 7000 ppm group were greater than those of the control group ($p<0.05$). The mean absolute and relative testicular weights of the 3500 and 7000 ppm males were less than the control group values ($p<0.05$). The mean absolute and relative uterine weights of the 3500 and 7000 ppm females were less than those of the control group (NS, $p<0.05$). Diffuse centrilobular hypertrophy in the liver was noted for both sexes in the 3500 and 7000 ppm groups. Hepatocellular single cell necrosis was evident in the livers of the 7000 ppm males. Increased numbers of corpora lutea were noted in the ovaries of the 3500 and 7000 ppm females. Histological examination of the vagina revealed that an increased number of females in the 7000 ppm group were in proestrus. **Possible adverse effect:** multifocal single cell necrosis in the liver. **Mouse Subchronic Dietary NOEL:** (M/F) 350 ppm ((M): 64.0 mg/kg/day, (F): 75.7 mg/kg/day) (based upon increased absolute and relative liver weights and lesions in the livers of both sexes in the 3500 ppm group); **Study supplemental** (no hematology was performed in the study). (Moore, 7/21/10)

Dog Subchronic Dietary Toxicity Study

** 53105-0063; 255869; "AE 0172747: 90-DayToxicity Study in the Dog by Dietary Administration"; (P. Kennel; Bayer CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 02162; 1/27/04); Four beagle dogs/sex/group received 0, 125, 750 or 4500 ppm in the diet for 90 days. However, after 29 days of treatment, the treatment level for the 4500 ppm group was reduced to 2250 ppm for the remainder of the study due to overt signs of toxicity ((M) 0, 4.5, 26.7, 124.0 mg/kg/day, (F) 0, 4.5, 28.5, 111.0 mg/kg/day). A male in the 4500/2250 ppm group was euthanized on day 38 for humane reasons. Treatment-related effects of uncoordinated movements, abnormal posture, wheelbarrowing and other abnormal behavior were noted prior to sacrifice. The mean body weight gains of both sexes in the 4500/2250 ppm group were less than those of the control group throughout the study. There was no apparent treatment-related effect on food consumption. The hemoglobin concentration, hematocrit percentage and MCV and MCH values for both sexes in the 4500/2250 ppm group were less than the control group values ($p<0.05$). The reticulocyte concentration of the 4500/2250 ppm females was increased over the course of the study ($p<0.05$). Various clinical chemistry parameters were statistically different from the control group values. However, these effects were not deemed to be of biological significance. The urinalysis did not reveal any treatment-related effects. Both eyes of one male in the 4500/2250 ppm group exhibited corneal opacity by the end of the treatment period. In the necropsy examination, the mean absolute and relative liver weights of both sexes in the 4500/2250 ppm group were greater than the control values (NS, $p<0.05$). The absolute and relative spleen weights of the 4500/2250 ppm males were greater than the values for the control group (NS). In the histopathology, diffuse cloudy swelling was noted in the

hepatocytes of the livers of 3/3 males in the 4500/2250 ppm group and of 1/4 and 4/4 females in the 750 and 4500/2250 ppm groups, respectively. Golden brown pigments were noted in the hepatocytes and Kupffer cells in the liver of 3/3 males in the 4500/2250 ppm group and of 1/4 and 2/4 females in the 750 and 4500/2250 ppm groups, respectively. Multifocal vaculolation of the zone glomerulosa in the adrenal glands was noted for the 3/3 of the males in the 4500/2250 ppm group. Increased number of digestion chambers were noted in various peripheral nerves of both sexes in the high dose group. **No adverse effect indicated. Dog Subchronic Dietary Toxicity NOEL:** (M) 750 ppm (26.7 mg/kg/day) (based upon treatment-related effects on hematology parameters and lesions in the liver, adrenal glands and nerves of the 4500/2250 ppm treatment group), (F) 125 ppm (4.5 mg/kg/day) (based upon lesions in the liver of the 750 ppm treatment group); **Study acceptable.** (Moore, 11/16/10)

METABOLISM STUDIES

53105-0048; 251783; "[Cyclohexyl-UL-^{14}C] AE 0172747: Rat Blood/Plasma Kinetics Study"; (J. Koester; Bayer CropScience AG, Development, Metabolism/Environmental Fate, 40789 Monheim am Rhein, Germany; Report No. MEF-04/437; 3/8/05); Four Wistar rats/sex/group were dosed orally by gavage with 5 or 1000 mg/kg of [Cyclohexyl-UL-^{14}C] AE-0172747 (batch no. BECH 1523, radiochemical purity: > 98%, chemical purity: > 98%, specific radioactivity: 7.05 MBq/mg). Blood samples were recovered from the tail vein at 0.5, 1, 2, 3, 4, 6, 8, 24, and then at 24-hour intervals up to 168 hours post-dose. The radioactivity in the whole blood and plasma was determined for each of the samples and pharmacokinetic parameters were calculated. The C_{max} values were 2.8 and 1.4 ug equiv./g in the blood and 5.1and 2.3 ug equiv./g in the plasma for the males and females, respectively, in the 5 mg/kg treatment group and 447 and 297 ug equiv./g in the blood and 649 and 455 ug equiv./g in the plasma of the males and females, respectively, in the 1000 mg/kg treatment group. The T_{max} values were 2.5 and 3.0 hours for the males and females, respectively, in the 5 mg/kg group and 6.5 to 6.6 and 8.6 to 8.8 hours for the males and females, respectively, in the 1000 mg/kg group. The $t_{1/2}$ elimination phase two values ranged from 38 to 64 hours for the 5 mg/kg treatment group and from 61 to 84 hours for the 1000 mg/kg group. The five metabolites which were identified were 4-hydroxy-benzylic alcohol, benzylic alcohol, 4,5-dihydroxy-AE 0172747, ketohydroxy-hexanoic acid, dihydroxy-benzophenone. Study supplemental. (Moore, 9/28/10)

53105-0048; 251784; "[Cyclohexyl-UL-^{14}C] AE 0172747: Absorption, Distribution, Excretion, and Metabolism in the Rat"; (J. Koester; Bayer CropScience AG, Development, Metabolism/Environmental Fate, 40789 Monheim am Rhein, Germany; Report No. MEF-04/512; 3/16/05); Four Wistar rats/sex/group were dosed orally by gavage with 5 or 1000 mg/kg of [Cyclohexyl-U-^{14}C] AE 0172747 (batch no. BECH 1517, radiochemical purity: >99%, chemical purity: 98%; specific activity: 7.05 MBq/mg). Unlabeled AE 0172747 (batch no. OE02/01, purity: 98.9%) was used to adjust the specific activity of the dosing preparations. Urine and feces were collected up to 7 days post-dose. The residual radioactivity in the tissues was measured at the time the animals were euthanized. Sixty nine percent of the administered dose was recovered in the feces of the male rats in contrast to females in which only 20% of the dose was recovered via that route. Conversely, 25 and 75% of the dose was recovered in the urine of the males and females, respectively. Eighty six and 93% of the administered dose was recovered within 24 hours post-dose for the males and females, respectively. The liver and kidneys were the two organs with the highest concentration of radiolabel. Identification of the radiolabeled moieties in the urine and feces revealed that a significant fraction of the recovered test material in the urine of the females was unmetabolized (43%). In the males, the percentage of unmetabolized parent compound recovered in the urine was less than 1%. In contrast, in the feces of the males and females, approximately 1% of the recovered radiolabel was parent compound, respectively. Hydroxylation of the cyclohexyl ring was the primary modification observed. **Study supplemental.** (Moore, 10/4/10)

53105-0048; 251785; "AE 0172747: Rat Blood/Plasma Kinetics Study"; (M. Odin-Feurtet; Bayer CropScience, BP. 153, F-06903 Sophia Antipolis, France; Study No. SA 02096; 10/17/02); Four Wistar rats/sex/group were dosed orally by gavage with 5 or 1000 mg/kg of [Phenyl-U-^{14}C]

AE-0172747 (batch no. Z 31053-4, radiopurity: 99.5%, specific activity: 65.19 mCi/mmole). Blood samples were recovered from the tail vein at 0.5, 1, 2, 3, 4, 6, 8, 24, and then at 24 hour intervals up to 168 hours post-dose. The radioactivity in the whole blood and plasma was determined for each of the samples and pharmacokinetic parameters were calculated. The C_{max} values were 8.1 and 5.2 ug equi./g in the blood and 14.5 and 9.5 ug equi./g in the plasma for the males and females, respectively, in the 5 mg/kg treatment group and 455 and 327 ug equi./g in the blood and 640 and 464 ug equi./g in the plasma of the males and females, respectively, in the 1000 mg/kg treatment group. The T_{max} values were 1 and 0.5 hours for the males and females, respectively, in the 5 mg/kg group and 5.0 and 2.5 hours for the males and females, respectively, in the 1000 mg/kg group. The terminal $t_{1/2}$ values were comparable for both the low and high dose treatment groups, ranging from 44 to 68 hours. **Study supplemental.** (Moore, 9/9/10)

53105-0049; 251786; "AE 0172747: Single Oral Low and High Dose Rat A.D.M.E. Study"; (M. Odin-Feurtet; Bayer CropScience, BP. 153, F-06903 Sophia Antipolis, France; Study No. SA 02092; 11/17/03, amended, 11/28/03); Four Wistar rats/sex/group were dosed orally by gavage with 5 or 1000 mg/kg of [Phenyl-U-^{14}C] AE 0172747 (batch no. Z 31053-4, radiopurity: 99.5%, specific activity: 65.19 mCi/mmole). AE 0172747 (unlabeled) (batch no. OE02/01, purity: 98.9%) was used to adjust the specific activity of the dosing preparations. Urine and feces were collected up to 7 days post-dose. The residual radioactivity in the tissues was measured at the time the animals were euthanized. Urine and fecal samples up to 48 hours post-dose were pooled and analyzed for metabolites by HPLC/MS. The urine was the primary path of excretion for the females with 84 and 74% of the administered dose recovered in the urine at the lower and higher doses, respectively. For the males, 27 and 53% of the administered dose was recovered in the urine for the lower and higher doses, respectively. At the lower dose level, 83 and 96% of the administered dose was excreted within the first 24 hours post-dose by the males and females, respectively. At the higher dose, 60 and 61% of the administered dose was excreted within the first 24 hours by the males and females, respectively. The liver and kidneys were the primary sites of recovery in the low dose group. At the high dose level, the skin was the primary site of recovery, followed by the liver, kidneys, stomach and contents, intestine and contents and blood. Identification of the radiolabeled moieties in the urine and feces revealed that a significant fraction of the recovered test material in the urine of the females in both the low and high dose groups was unmetabolized (5: 77%, 1000: 65%). In the males, the unmetabolized parent compound constituted 11 and 46% of the recovered radioactivity in the urine of the low and high dose groups, respectively. In contrast, in the feces of the low dose males and females, 1.5 to 4% of the recovered radiolabel was parent compound, respectively. In the high dose group, these percentages increased to 34 and 22%, respectively. Hydroxylation of the cyclohexyl ring was the primary modification observed. **Study supplemental.** (Moore, 9/30/10)

MECHANISTIC STUDIES

53105-0036; 251755; "Effect of Tyrosinaemia on Pregnancy and Embryo-Fetal Development in the Rat"; (P. Kennel; Bayer CropScience, BP 153, F-06903 Sophia Antipolis Cedex, France; Study No. SA 05192; 1/13/06); Twenty three mated female Sprague-Dawley rats/group were dosed orally with (Group I) 0 (vehicle: demineralized water) by gavage, (Group II) 20000 ppm of L-tyrosine in the diet from day 6 through day 21 of gestation, (Group III) 10 ug/kg/day of NTBC (inhibitor of 4-hydroxyphenylpyruvic acid dioxygenase, batch no. MKH132222-3-2, purity: 99.7%) by gavage from day 6 through day 20 of gestation, and (Group IV) 20000 ppm of L-tyrosine in the diet and 10 ug/kg/day of NTBC by gavage for the same respective durations as in Groups II and III. One female in Group III was euthanized for humane reasons on day 13. The mean body weight gains for the dams in Groups III and IV were less than that of the control group between days 6 and 8. Thereafter no treatment-related effect was apparent. There was no treatment-related effect upon food consumption. The various treatments resulted in elevated levels of tyrosine in the serum. Treatment with the enzyme inhibitor together with the supplementation of the amino acid increased the tyrosine levels at least 7 and 13 times, respectively, above the levels observed for the individual treatments alone. A treatment-related effect was noted on the ossification of the bones of the fetuses in Group IV. However, the study data did not substantiate that the effect of increased skeletal anomalies and variation observed for tembotrione possibly resulted from elevated tyrosine levels in the serum. **Study supplemental.** (Moore, 8/2/10)

53105-0051; 251790; "AE 0172747: Effects on Blood Coagulation Parameters with and without Administration of Vitamin K1"; (O. Blanck; Bayer CropScience AG, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 04296; 4/15/05); Eight male Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methyl cellulose), 1000 mg/kg/day or 1000 mg/kg/day + vitamin K1, 10 mg/kg/day (subcutaneous injection) of AE 0172747 (tembotrione technical) (batch no. PFI 0254; purity: 95.4%) for 3 days. No deaths resulted from the treatment. Food consumption was reduced for the animals in the treated groups over the 3-day treatment period. In the hematology evaluation of clotting factors, the prothrombin and activated partial thromboplastin times were prolonged for the animals only treated with the test material. Treatment with vitamin K1 largely reversed the effect on these two parameters. Among the extrinsic clotting factors, assays for II, VII and X demonstrated a prolonged clotting time for the AE 0172747-alone treated animals ($p<0.01$). These effects were ameliorated by treatment with vitamin K1. For the intrinsic clotting factors VII, IX and XII, assays demonstrated prolonged clotting times for the AE 0172747-alone treated animals ($p<0.01$). Likewise, treatment with vitamin K1 reversed these effects. **Study supplemental.** (Moore, 10/5/10)

53105-0051; 251791; "AE 0172747: Effect on Blood Tyrosine Level in Pregnant Rabbit after Oral Administration by Gavage"; (O. Blanck;; Bayer CropScience AG, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 03315; 6/15/04); Six pregnant female New Zealand white rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methyl cellulose) or 10 mg/kg/day of AE 0172747 (tembotrione technical) (batch no. PFI 0195, purity: 95.0%) from day 6 through day 28 of gestation. Blood samples were collected from each animal on gestation days 4, 10, 15, 22 and 29 and analyzed for tyrosine levels. No deaths resulted from the treatment. No treatment-related clinical signs were evident. A mean peak serum tyrosine level was observed in the treated animals on day 10 of gestation. Overall, peak levels for the 10 mg/kg animals ranged from 3.3 to 6.5 times the levels observed in the control animals during the dosing period. No adverse effects on the fetuses was reported. **Study supplemental.** (Moore, 10/5/10)

53105-0051; 251792; "AE 1417268, AE 0456148, and AE 1392936: Assessment of HPPDase Inhibition in the Rat (Parts A, B & C); (M. Totis; Bayer CropScience AG, BP 153, 06903 Sophia Antipolis Cedex, France; Study Nos. SA 04132 and SA 04313; 3/7/05); Three male Wistar rats/group were dosed orally by gavage with 0 (vehicle: polyethylene glycol 400) or 10 mg/kg of either AE 1417268 (batch no. 2003BRP003-284, purity not reported), AE 0456148 (batch no. OD05/01, purity not reported), AE 1392936 (batch no. LSMI 1-2-34, purity not reported0 or AE 0172747 (batch no. PFI 0195, purity not reported). The serum levels of L-tyrosine were determined up to 72 hours post-dose. Among the metabolites, only AE 1417268 demonstrated an increase in L-tyrosine levels above that of the control group. The Cmax which was achieved was 75 mg/l in comparison to 316 mg/l observed for AE 0172747. The tmax times were 8 hours for AE 1417268 and 24 hours for AE 0172747. The area under the curve was 5 times greater for AE 0172747 than AE 1417268. **Study supplemental.** (Moore, 10/6/10)

53105-0051; 251793; "*In Vitro* Inhibition of HPPDase using Liverbeads™ from Different Species"; (M. Totis; Bayer CropScience AG, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 05068; 8/16/05); Liverbeads™, in which hepatocytes from rat, mouse, rabbit, dog and humans were seeded in culture medium, were incubated up to 4 hours in the presence and absence of AE 0172747 (batch no. PFI 0254, purity: 94.7%) at a final concentration of 120 uM and with and w/o a tyrosine supplement (100 mg/l). The concentrations of tyrosine and 4-hydroxyphenyl lactic acid (4-HPLA) were assayed in the medium of each preparation at 0, 2 and 4 hours after the initiation of the incubation. In the analysis of the tyrosine content, the concentration of the precursor in the medium declined the most in the mouse hepatocyte assay in the absence of AE 0172747 with or w/o the tyrosine supplement. When the test material was added to the assay, tyrosine content remained constant. For the other four species, the results were equivocal. For humans, in the absence of AE 0172747, the tyrosine content actually rose or remained relatively constant throughout the 4-hour incubation with or w/o the tyrosine supplement. With the addition of the test material, the tyrosine content increased in the basal incubation (no tyrosine supplement) in contrast to remaining constant in the tyrosine-supplemented assay. In the assays using the rat and rabbit hepatocytes, the concentration of

tyrosine increased in the presence or absence of AE 0172747 under basal conditions. For the rat, when the tyrosine content was supplemented, the tyrosine content declined in the presence or absence of the test material. In the assay with the rabbit hepatocytes, when tyrosine was supplemented, the tyrosine content remained constant in the presence or absence of the test material. For the dog, there was a slight decline in the tyrosine content in the absence of the test material with and w/o the supplemented tyrosine. When AE 0172747 was added, the tyrosine content remained constant (basal conditions) or increased (tyrosine supplemented). In the 4-HPLA analysis, recovery of the metabolite was noted at all assay time points for the mouse hepatocytes. For the human hepatocytes, the metabolite was present in the medium to which AE 0172747 was added after 2 hours of incubation. The concentration of the metabolite was greater in the tyrosine supplemented assays for both species. The metabolite was not found in any of the rat, dog or rabbit hepatocyte assays w/o tyrosine supplementation. When the assays were supplemented with tyrosine, 4-HPLA was recovered in all of the preparations by the end of the incubation period. These data indicated that in the presence of AE 0172747, the putative metabolic pathway of tyrosine was altered, resulting in the formation of 4-HPLA. The mouse hepatocytes metabolized the precursor more rapidly than did the other species, resulting in the highest concentrations of 4-HPLA in the medium. Human hepatocytes demonstrated the second most active rate of metabolism. For the other species, the rate of metabolism to 4-HPLA was similar. **Study supplemental.** (Moore, 10/7/10)

53105-0053; 251811; "Effects of Diets Enriched with Tyrosine on Selected Organs in Rats"; (O. Blanck; Bayer CropScience AG, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 05207; 8/1/06); Ten Wistar rats/sex/group were dosed orally by gavage with either 0 (Groups 1 and 2) or 10 ug/kg/day of 2-(2-Nitro-4-Trifluoromethyl-Benzoyl)-1,3-Cyclohexanedione (NTBC) (batch nos. MKH1322-3-2, MKH1322-4-1; purity: 99.7%, 99.9%) for four weeks (Groups 3 and 4). In addition, the diet of Groups 2 and 4 were supplemented with 20000 ppm of L-tyrosine throughout the treatment period. One female in Group 3 died on day 3 of the study due to accidental trauma. There was no treatment-related effect on the mean body weights or food consumption of the study animals. Addition of L-tyrosine to the diet resulted in a minimal increase in the serum tyrosine levels. Treatment with the HPPDase inhibitor resulted in a 15 to 25-fold increase of tyrosine in the serum with or w/o the tyrosine supplement in the diet. In the ophthalmological examination, corneal edema and opacity were noted in 9 and 10 males, respectively, in Group 4 (NTBC + supplemental tyrosine). Three females in Group 4 demonstrated corneal opacity as well. Three males in Group 4 also suffered congestion of the iris. No treatment-related ocular effects were apparent for animals in any of the other groups. The mean relative liver weights of both sexes in Group 4 (NTBC + supplemental tyrosine) were greater than the control values ($p<0.05$). In the histopathological evaluation, interstitial inflammation was noted in the pancreas of the 1 male in Group 2 (supplemental tyrosine alone) and 3 males and 5 females in Group 4 (NTBC + supplemental tyrosine). Colloidal alteration in the thyroid glands was evident for 1 male each in Groups 2 (supplemental tyrosine alone) and 3 (NTBC alone) and 6 males in Group 4 (NTBC + supplemental tyrosine). Keratitis was noted in the eyes of 1 male in Group 1 (control) and 9 males and 1 female in Group 4 (NTBC + supplemental tyrosine). The study was performed for the purpose of examining the role of excessive serum tyrosine levels in the pathogenesis of ocular lesions. The serum tyrosine levels were elevated for both sexes in the Groups 3 and 4 after treatment with NTBC. However, only the males in Group 4 demonstrated corneal edema. Apparently, a high tyrosine level was not the sole factor in causing the ocular lesion. **Possible adverse effect:** corneal edema and opacity. **Study supplemental** (mechanistic study in which the test material was not used). (Moore, 10/11/10)

53105-0055; 251813; "Effects of Tyrosinaemia on Selected Organs in Rats"; (O. Blanck; Bayer CropScience, BP 153, 06903 Sophia Antipolis Cedex, France; Study No. SA 05330; 8/1/06); Five Wistar rats/sex/group were dosed orally by gavage with either 0 (Groups 1 and 2) or 10 ug/kg/day of 2-(2-Nitro-4-Trifluoromethyl-Benzoyl)-1,3-Cyclohexanedione (NTBC) (batch no. MKH1322-4-1; purity: 99.9%) for four weeks (Groups 3 and 4). In addition, the diet of Groups 2 and 4 were supplemented with 20000 ppm of L-tyrosine throughout the treatment period. No deaths occurred during the treatment period. There was no treatment-related effect on the mean body weights. The mean food consumption of both sexes in Group 4 (NTBC + supplemental tyrosine) was less

than that of the control group ($p<0.05$, NS). Addition of L-tyrosine to the diet resulted in a 3 to 4-fold increase in the serum tyrosine levels. Treatment with the HPPDase inhibitor resulted in a gradual increase in the serum tyrosine levels until a 3 to 6-fold increase over the control levels of both sexes was achieved by the 4th week of the study. When both NTBC treatment and supplemental tyrosine were combined, the serum tyrosine concentrations were elevated 26 and 17-fold for the males and females, respectively, resulting in serum concentrations of 1980 and 890 nml/ml. When the animals in Group 4 were fasted overnight, the females demonstrated a 2-fold increase in the serum tyrosine levels. Likewise, both sexes in Group 3 (NTBC alone) were fasted had an almost 5-fold increase in the serum tyrosine concentrations when they were fasted. In contrast, the tyrosine concentration in the serum of the Group 2 animals decreased by 50 to 70% after the overnight fast. In the ophthalmological examination, corneal edema and opacity were noted in all 5 of the males, in Group 4 (NTBC + supplemental tyrosine). One female in Group 4 demonstrated corneal opacity as well. No treatment-related ocular effects were apparent for animals in any of the other groups. The mean relative liver weights of both sexes in Group 4 (NTBC + tyrosine) were greater than the control values (NS, $p<0.05$). In the histopathological evaluation, acinar degeneration was noted in the pancreas of 1 male, each, in Groups 1, 2 and 3 and 3 males in Group 4, and the pancreas of 1 and 5 females in Groups 3 and 4, respectively. Colloidal alteration in the thyroid gland was evident for 3 males in Group 4. Keratitis was noted in the eyes of all 5 males and 1 female in Group 4. The study was performed for the purpose of examining the role of excessive serum tyrosine levels in the pathogenesis of ocular lesions. In this study, the serum tyrosine levels of the males in Group 4 (NTBC + supplemental tyrosine) were more than twice the level observed for the females in this group, 1981 nmol/ml as compared to 892 nmol/ml. When the animals were fasted, the serum concentration of tyrosine rose to 1422 nmol/ml for the females. Fasting overnight resulted in a significant increase in the tyrosine levels for both sexes in Group 3 (NTBC alone) as well. These results correlate with those reported in Study No. SA 05207 (53105-0053, rec. no. 251811) in which the animals were fasted prior to the blood sampling. The incidence of corneal edema and opacity in the males of Group 4 correlated with the elevated serum tyrosine levels experienced by these animals throughout the treatment period. **Possible adverse effect:** corneal edema and opacity. **Study supplemental** (mechanistic study in which the test material was not used). (Moore, 10/12/10)

STUDIES ON METABOLITES AND ANALOGUES

Rat acute oral toxicity studies

53105-0025; 251727; "AE 0456148: Acute Toxicity in the Rat after Oral Administration"; (R. Eiben; Bayer HealthCare AG, PH-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01510; 10/6/04); Six female Wistar rats were dosed orally by gavage with 2000 mg/kg of AE 0456148 (tembotrione metabolite) (batch no. ABJ1204-PFI, purity: 99.0%) (vehicle: 2% Cremophor EL in demineralized water). No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were evident. LD50 (F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/8/10)

53105-0025; 251728; "AE 1417268: Acute Toxicity in the Rat after Oral Administration"; (M. Schungel; Bayer HealthCare AG, PH-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01702; 12/15/04); Six female Wistar rats were dosed orally by gavage with 2000 mg/kg of AE 1417268 (tembotrione analogue) (batch no. KTS 10124-32-2; purity: 97.9%) (vehicle: aqueous 2% Cremophor EL). No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were evident. LD50 (F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/8/10)

53105-0025; 251729; "AE 1392936: Acute Toxicity in the Rat after Oral Administration"; (M. Schungel; Bayer HealthCare AG, PH-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01979; 4/20/05); Six female Wistar rats were dosed orally by gavage with 2000 mg/kg of AE 1392936 (tembotrione analogue) (batch no. LSMI 1-2-34; purity: 94%) (vehicle: aqueous 2% Cremophor EL). No deaths resulted from the treatment. No treatment-related

clinical signs were evident. In the necropsy examination, no treatment-related lesions were evident. LD50 (F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/9/10)

Rat Dermal Toxicity Studies

53105-0025; 251732; "AE 0456148: Acute Toxicity in the Rat after Dermal Application"; (M. Schungel; Bayer HealthCare AG, PH-R&D Toxicology, 42096 Wuppertal, Germany; Report No. AT02537; 10/21/05); The skin of five Wistar rats/sex was exposed to 2000 mg/kg of AE 0456148 (tembotrione metabolite) (batch no. FSD0415, purity: 95.9%) for 24 hours under a semi-occlusive wrap. No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were noted. Reported LD50 (M/F) > 2000 mg/kg; Toxicity Category not assigned; **Study unacceptable**, possibly upgradeable to acceptable with additional information of how well the test material was moistened. (Moore, 7/9/10)

Rabbit Primary Eye Irritation Study

53105-0025; 251737; "AE 0456148: Acute Eye Irritation on Rabbits"; (M. Schungel; Bayer HealthCare AG, PH-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01860; 2/21/05); The eyes of 3 New Zealand White rabbits were treated by ocular instillation with 0.1 g/eye of AE 0456148 (tembotrione metabolite) (batch no. ABJ1104-PFI, purity: 99.0%) Corneal opacity, grades 2 (1/3) and 1 (1/3), was evident at 24 hours post-dose, diminishing to grade 2 (1/3) at 48 hours, grade 1 (1/3) at 72 hours and clearing by 7 days. No iritis was noted during the observation period. Conjunctival redness, grade 3 (3/3), was evident at 24 hours post-dose, diminishing to grades 2 (1/3) and 1 (2/3) at 48 hours, grade 2 (1/3) at 72 hours and clearing by 7 days. Chemosis, grades 2 (2/3) and 1 (1/3), was noted at 24 hours, diminishing to grade 1 (2/3) at 48 hours and clearing by 72 hours. Toxicity Category III; **Study acceptable.** (Moore, 7/12/10)

Rabbit Primary Dermal Irritation Study

53105-0025; 251740; "AE 0456148: Acute Skin Irritation/Corrosion on Rabbits"; (M. Schungel; Bayer HealthCare AG, PH-R&D Toxicology International, 42096 Wuppertal, Germany; Report No. AT01805; 1/24/05); The skin of 3 New Zealand White rabbits were exposed to 0.5 g/site, one site/animal, of AE 0456148 (tembotrione metabolite) (batch no. ABJ1104-PFI, purity: 99.0%) for 4 hours under a semi-occlusive wrap. The test material was moistened with water. No erythema nor edema was evident throughout the 72-hour observation period. Toxicity Category IV; **Study acceptable.** (Moore, 7/12/10)

Guinea Pig Dermal Sensitization Study

53105-0026; 251743; "AE 0456148: Local Lymph Node Assay in Mice"; (H.-W. Vohr; Bayer HealthCare AG, PH-R&D Toxicology International, 42096 Wuppertal, Germany; Report No. AT01750; 1/5/05); The dorsal skin on the ears of 6 female NMRI mice/group was treated by topical application with 25 ul/ear/day of 0 (vehicle: dimethylformamide), 1, 3, or 10% of AE 0456148 (tembotrione metabolite) (batch no. ABJ1104-PFI, purity: 99.0%) for 3 days. On day 4, each animal was euthanized. The draining auricular lymph nodes were removed. The nodes were weighed and then crushed through a sieve and the number of cells/ml was determined. An 8 mm diameter section of ear was punched out and weighed. A stimulus index (SI) was determined by dividing the mean node and ear weights, change in ear thickness and nodal cell counts of the treated groups by the mean values of the vehicle control. A treatment-related increase in lymph node cell count, ear swelling and ear weight was noted at the highest treatment level ($p<0.05$). No positive control study data were not included in the study. **Study acceptable**. (Moore, 7/15/10)

Gene Mutation

** 53105-0042; 251767; " AE 0456148: Salmonella/Microsome Test, Plate Incorporation and Preincubation Method'; (B. Herbold; Bayer HealthCare AG, PH-R&D-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01610; 10/28/04); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 0456148 (tembotrione metabolite) (batch no. ABJ1204-PFI; purity: 99%) at levels ranging from 16 to 5000 µg/plate in two trials

under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/26/10)

** 53105-0043; 251768; " AE 1417268: Salmonella/Microsome Test, Plate Incorporation and Preincubation Method'; (U. Wirnitzer; Bayer HealthCare AG, PH-R&D-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01713 12/16/04); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 1417268 (tembotrione metabolite) (batch no. KTS 10124-32-2; purity: 97.9%) at levels ranging from 16 to 5000 µg/plate in two trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/26/10)

** 53105-0043; 251769; " AE 1392936: Salmonella/Microsome Test, Plate Incorporation and Preincubation Method'; (U. Wirnitzer; Bayer HealthCare AG, PH-R&D Toxicology International, 42096 Wuppertal, Germany; Report No. AT02552; 10/27/05); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 1392936 (tembotrione metabolite) (batch no. LSMI 1-234; purity: 94.0%) at levels ranging from 16 to 5000 µg/plate in two trials under conditions of (-/+) activation for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation under conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/26/10)

** 53105-0043; 251771; "AE 0456148: V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare AG, PH-R&D-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01738; 12/10/04); (B. Herbold; Bayer HealthCare, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T 8072081; 7/16/03); Chinese hamster V79 cells were exposed to AE 0456148 (tembotrione metabolite) (batch no. ABJ1204-PFI; purity: 99%) at concentrations ranging from 55 to 3520 µg/ml for 5 hours at 37° C in the 3 trials w/o activation and in the 2 trials with activation. Each treatment level was cultured in duplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in any of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/30/10)

** 53105-0043; 251772; "AE 1417268: Mutation at the Thymidine Kinase (*tk*) Locus of Mouse Lymphoma L5178Y Cells (MLA) Using the Microtitre Fluctuation Technique"; (G. Semino; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 2014/89; 10/26/05); Mouse lymphoma L5178Y cells were treated with AE 1417268 (tembotrione metabolite) (batch no. KTS 10124-73-8; purity: 99.3%) at concentrations ranging from 480 to 4724 ug/ml under conditions of activation and non-activation for 3 hours at 37° C in the 1st trial and for 3 hours under conditions of activation and 24 hours under conditions of non-activation in the 2nd trial. Duplicate cultures/treatment level were included in the study. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Cell survival and viability and mutation frequency for each treatment level were determined and compared to those of the solvent control. In the 2nd trial, the 4724 ug/ml treatment level In the non-activated assay

demonstrated an increased mutation frequency ($p<0.05$). A positive trend test was noted for this assay. However, the data were deemed not to indicate a positive mutagenic response. This decision was based in part on the recommendation of the Mouse Lymphoma workgroup which stipulated that a response had to exceed the concurrent control by 126 mutants/10^6 viable cells (Global Evaluation Factor) in order for it to be a mutagenic effect. The report author acknowledged that a positive response was evident. However, the response occurred at a concentration of 10 uM (4724 ug/ml) and excessive precipitation of the test material was present in the incubation preparation. The biological significance of the response was deemed to be questionable. For the assays with the S9 fraction, there was no dose-related increase in mutation frequency. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/31/10)

** 53105-0043; 251774; "AE 1392936: V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare AG, PH-R&D Toxicology International, 42096 Wuppertal, Germany; Report No. AT02433; 8/26/05); Chinese hamster V79 cells were exposed to AE 1392936 (tembotrione metabolite) (batch no. LSMI 1-2-34; purity: 94.0%) at concentrations ranging from 45 to 1440 µg/ml for 5 hours at 37° C with and w/o activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in either of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 9/1/10)

Chromosome Effects

** 53105-0043; 251775; "AE 0456148: *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells"; (B. Herold; Bayer HealthCare AG, PH-R&D-PD Toxicology International, 42096 Wuppertal, Germany; Report No. AT01906; 2/25/05); Chinese hamster V79 cells were exposed to AE 0456148 (tembotrione metabolite) (batch no. ABJ1204-PFI; purity: 99.0%) at 37° C. Cells were exposed to concentrations of the test material ranging from 900 to 3600 ug/ml for 4 hours under conditions of (+/-) activation and harvested after 18 hours of total incubation time or to a concentration of 3600 ug/ml and harvested after 30 hours of total incubation time. In a second assay, cells were exposed to concentrations of the test material ranging from 900 to 3600 ug/ml for 18 hours under conditions of nonactivation. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. No treatment-related increase in chromosomal aberrations was evident under conditions of (+/-) activation. The positive controls were functional. **No adverse effect was evident. Study acceptable**. (Moore, 9/2/10)

** 53105-0044; 251776; "AE 1417268: Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes"; (T.S. Kumaravel; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 2014/88; 10/6/05); Phytohemogglutinin-treated human lymphocytes (whole blood) were treated with AE 1417268 (tembotrione metabolite) (batch no. KTS 10124-73-8; purity: 99.3%) at concentrations ranging from 10 to 4724 ug/ml in the 1st trial and from 634 to 4724 ug/ml in the 2nd trial under conditions of both non-activation and activation at 37° C. In the 1st trial, under conditions of both non-activation and activation, the cells were exposed to the test material for 3 hours, washed and then incubated for an additional 17 hours. In the 2nd trial, in the non-activated assay, the cells were exposed to the test material for 20 hours. The cells in the activated assay were treated in the same manner as in the 1st trial. A liver homogenate S9 fraction from male rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no increase in the incidence of chromosomal aberrations under conditions of activation or non-activation. **No adverse effect indicated.** The positive controls were functional for both activation and non-activation. **Study acceptable.** (Moore, 9/3/10)

** 53105-0044; 251777; "AE 1392936 00 1C94 0001: *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells"; (M. Thum; Bayer HealthCare AG, PH-R&D Toxicology International, 42096 Wuppertal, Germany; Report No. AT02214; 7/12/05); Chinese hamster V79 were exposed to concentrations of AE 1392936 (tembotrione metabolite) (batch no. LSMI 1-2-34; purity: 94.0%) ranging from 350 to 1400 ug/ml with and w/o activation for 4 hours at 37° C. Cells were harvested

at 18 or 30 hours after the beginning of the treatment. In addition, cells were exposed to the test material for 18 hours at concentrations ranging from 350 to 1400 ug/ml w/o activation. One trial was performed. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. No treatment-related increase in chromosomal aberrations was evident under conditions of (+/-) activation. The positive controls were functional. **No adverse effect was evident. Study acceptable**. (Moore, 9/3/10)